Amendments to the Drawings

The first three sheets of drawings containing formula I-III are already present in the specification on pages 1-2 as pointed out by the examiner, and thus the content of drawing sheets 1-3 is repetitive and redundant. The applicant has corrected this issue by removing drawing sheets 1-3 in the drawings, and three original drawings of Figure 1-3 are resubmitted and enclosed with this reply.

Remarks/Arguments

Re: Claim Rejections –35 USC §112

1. The applicant would like to point out that Claim 33 is for the use of a particular polymorph composition of fluvastatin sodium, not fluvastatin sodium compound itself. When a given polymorph form of fluvastatin sodium is administered and goes into the blood circulation in human beings or any mammals, the fluvastatin sodium molecule is in a solution state, its biological activity is independent on the solid state properties of fluvastatin sodium. It is well established in the art that fluvastatin sodium is useful for the prevention or treatment of recited diseases. Claim 33 is very narrow claim and it is limited to only the use of anhydrous amorphous form of fluvastatin sodium. The use of a particular new polymorph form of any given compounds is allowable matter, as demonstrated in cited reference by Horvath, U. S. Patent No. 6,124,340 (see Claim 19).

2. Claim 1 reciting the term "novel" has been amended and the term "novel" has been removed. The amended Claim 1 is now a definite and distinct claim of the subject matter, and it is allowable subject matter. Claim 1 is further amended to limit its scope. Claims 4 and 7 are cancelled.

3. Claim 33 is cancelled.

Re: Claim Rejections-35 USC § 101

Claim 33 is cancelled.

Re: Claim Rejections-35 USC § 102

In view of the examiner's rejections on Claims 1, 4, 7, 18, 21, 23-27, 28 and 31-33 under 35 U. S. C. 102(b), the applicant retains the right to present amended claims or original claims (1, 8, 13-18 and 23-28). Applicant presents following remarks and arguments pointing out the specific distinctions and patentable novelty to render these claims.

The applicant like to provide a very clear and convincing evidence to establish that the prior art (Horvath, US 6,124,340) product is completely different from the claimed product and that anticipation cannot be established based on the prior art.

The claimed product is pure or essentially pure anhydrous amorphous form of fluvastatin dosium. It is well established in the art that X-ray powder diffraction technique is able to detect about 2-5% or more crystalline materials in an amorphous composition (see attached reference by Rahul Surana, Powder Diffraction, March 2000, vol. 15, Issue 1, pp. 2-6). Therefore, the claimed product is anhydrous amorphous form containing less than 5% crystalline fluvastatin sodium. The X-ray powder diffraction pattern of the claimed product is shown in Figure 3 of the instance invention.

Meanwhile, according to Horvath, US 6,124,340, the prior art product is "a mixture of a crystalline form and amorphous material" in col. 2 and contains "~50% crystallinity for form A" **in col. 8 (lines 5-25)**. More specifically, the cited reference (US6,124,340) teaches that lyophilized fluvastatin sodium form A is a mixture of amorphous and crystalline materials and contains about 50% amorphous material and about 50% crystalline form A of fluvastatin sodium, as disclosed in col. 2, col. 7, col. 8 and col. 9. The X-ray powder diffraction pattern of the prior art product (form A obtained by lyophilization) is shown in Figure 3 of the reference (see sheet see sheet 2 in reference US6,124,340). Additionally, the prior art product is amorphous and crystalline fluvastatin sodium hydrate as it is obtained by lyophilization in aqueous solution wherein water is used as a solvent. The applicant respectively asks the examiner to go through the teachings in col. 8 (lines 5-25) and Figure 3 of the cited reference "340".

The X-ray powder diffraction pattern of the prior art product, as shown in Figure 3 (see sheet 2 in reference US6,124,340), displays many sharp and strong peaks, indicating the presence of a significant amount (~50%) of crystalline fluvastatin sodium in the sample. However, the X-ray powder diffraction pattern of the claimed product, as shown in Figure 3 of the instant invention, lacks any discernible peaks and displays only

one or more broad diffuse halos, indicating an essentially pure amorphous material (e.g., less than 5% crystalline stuffs). Therefore, the claimed product and prior art product are clearly different and patentably distinct, as demonstrated by their X-ray powder diffraction patterns, teachings and disclosures in the prior art and instant invention.

The structural formula in col. 1 is just a chemical structure of fluvastatin sodium molecule, which is not relevant to any physical forms of fluvsattin sodium. The form A in col. 2 is a mixture of amorphous and crystalline fluvastatin sodium hydrate (~50%), as described above. The teachings and disclosures on characteristic nature of the prior art product **in col. 8 (lines 5-25)** and Figure 3, are critical evidences for the establishment of the distinct difference between the prior art product and the claimed product.

Claims 18 and 24-27 of instant invention are drawn to a process of preparation of the anhydrous amorphous fluvastatin sodium in acetonitrile or alkanol. In col. 3-4 (lines 15-25), reference US6,124,340 stated that "Any non-B form (an error of non form B) of fluvastatin sodium, e.g., amorphous material or fluvastatin sodium form A, can initially be partly dissolved in the organic solvent and water mixture and stirred until the desired form B is formed...". The reference teaches processes to prepare crystalline fluvastatin sodium form B, as shown in col. 3-4. The reference fails to disclose or teach any elements related to the processes to prepare anhydrous amorphous fluvastatin sodium. The applicant respectively reminds the examiner that processes for preparation of anhydrous amorphous fluvastatin sodium of the instant invention is a completely different subject matter from the processes for preparation of crystalline fluvastatin sodium form B of the prior art. Even some parameters and conditions (e.g., starting materials and solvents) in their respective processes may be similar, other parameters and conditions are different so that their respective processes lead to the formation of completely different products.

More specifically, the patent "340" only teaches the use of ethanol or acetonitrile and water and any physical forms except form B as starting materials to make crystalline fluvastatin sodium form B, as disclosed in methods (i), (ii) and (iii), and it fails to teach or suggest the use of ethanol or acetonitrile to make the anhydrous amorphous form of fluvastatin sodium. By following the process in the prior art, anhydrous amorphous

fluvastatin sodium cannot be produced; instead, crystalline fluvastatin sodium form B will be obtained. The prior art is not intended to disclose, appreciate or recognize anhydrous amorphous form of fluvastatin sodium.

In summary, in the prior art, nothing is remotely suggested as the existence of an amorphous composition comprising over 95% w/w anhydrous amorphous form or pure anhydrous amorphous form of fluvastatin sodium.

Meanwhile, the subject matter of the current invention is to disclose a new, particularly distinct physical form physical form of fluvastation sodium, e.g., anhydrous amorphous form of fluvastatin sodium. The instant claim 1 covers a new amorphous composition, which has never been produced, disclosed, appreciated, and recognized in the prior art, and which cannot be produced using the process in the prior art.

In conclusion, the prior art reference (US 6,124,340) does not teach any elements of the instant claim 1. The compositions or elements thereof in instant claim 1 have not existed or have not occurred to any certainty in prior art reference, and claim 1 patentably distinguishes from the prior art product. In summary of above remarks and arguments, anticipation cannot be established by reference US 6,124,340 with regarding to the instant claim 1, and instant claim 1 is allowable subject matter.

Claim 1 is amended to particularly point out definitely and distinctly claiming the subject matter, by including "wherein it is free of water and lacks any discernible peaks". Claim 1 are further combined with claim 4 and thus claim 4 is cancelled. The amended claim 1 is a much narrower claim than the original claim.

In addition, Claims 2-7, 9-12, 19-22 and 29-31 are cancelled due to substantial duplicates or election without traverse.

Re: Claim Rejections-35 USC § 103

The applicant would like to point out there is an error in the office action summary by stating that "this application currently names joint inventors". There is only one inventor in this application. The examiner has acknowledged that this is a mistake and the applicant does not need to respond this paragraph in a telephone conversation between the applicant and the Examiner, dated on December 19, 2006.

In view of the examiner's rejections on Claims 1, 4, 7, 11, 13-18, 21, 23-28 and 31-33 under 35 U. S. C. 103(a), the examiner fails to establish a *prima facie* case of obviousness, and thus the applicant retains the right to present amended claims or original claims 1, 8, 13-18 and 23-28. The applicant presents following remarks and arguments.

In order to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Secondly, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. (MPEP, *supra* note 39, at § 2142) and (In re Vaeck, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In addition, according to MPEP-2141, in consideration and determination of obviousness under 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) Claimed invention must be considered as a whole;

(B) References must be considered as a whole (and they must suggest the desirability, and thus obviousness, of making the proposed combination);

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

In Office Action Summary dated on June 8, 2006, the Examiner acknowledges that fluvastatin sodium, rosuvastatin calcium, pitavastatin calcium and atorvastatin calcium are made independently and used independently, that they are not art-recognized equivalents and that they are separately classified and patentably distinct. The reference by Kumar et al., WO 00/71116 teaches a process to make amorphous atorvastatin calcium, and doesn't actually teach or suggest, on its face, the new subject matter being

patented. The chemical structure of atorvastatin calcium is completely different from that of fluvastatin sodium. It is well established in the art that it is impossible to predict the polymorphism of the new compound, and that it is impossible to predict which parameters and conditions are suitable to produce any polymorphs forms of any compounds, including amorphous form. There are numerous parameters and conditions involved in producing amorphous form of a given compound. This situation is demonstrated in a recent article by Alexandra Goho, Science news online, 2004, vol.166, No. 8, p. 122 (refer to the attached reference). In addition, Horvath (US6,124,340) fails to teach or disclose any elements of anhydrous amorphous fluvastatin sodium and failed to produce the claimed product by lyophilization. This reference further teaches away from the production of the instant claim 1 by disclosing that a pure amorphous fluvastatin sodium cannot be obtained by lyophilization and only about 50% form A and amorphous material will be obtained by this process. It is well established in the art that lyophilization is the most common method to produce pure amorphous form of pharmaceutical agents. For example, pure amorphous atorvastatin calcium as cited by the examiner can be produced by lyophilization method (refer to WO2006046109). Therefore, there is a lack of teachings, suggestions, proper motivation or desirability to combine references cited by the examiner.

It is well settled that the prior art must teach or suggest the desirability of the modification proposed by the examiner, and there are no teachings or suggestions in the cited reference regarding existence of the claimed product and processes to produce the said product. Lacking such teachings or suggestions in the prior art, the examiner's rejection is based upon impermissible hindsight. The examiner hasn't met the burden of proving *a prima facie case* of obviousness of the claimed invention.

In summary, the subject matter of claimed invention is non-obviousness, and claims 1, 8, 13-18 and 23-28 are patentable over references cited. Therefore, applicant respectfully asks the examiner to reconsider claims 1, 8, 13-18 and 23-28.

Re: Duplicate Claims

In view of examiner's suggestions, claims 7, 11, 21 and 31 are cancelled.

1. Claim 7 is cancelled since this claim is a substantial duplicate of claim1.
2. Claim 11 is cancelled since this claim is a substantial duplicate of claim 8.
3. Claim 21 is cancelled since this claim is a substantial duplicate of claim 18.
4. Claim 31 is cancelled since this claim is a substantial duplicate of claim 28.

Respectfully submitted,
Mai De Ltd.

By _____
Hui Min He-Huang
Tel: (508) 873-3038

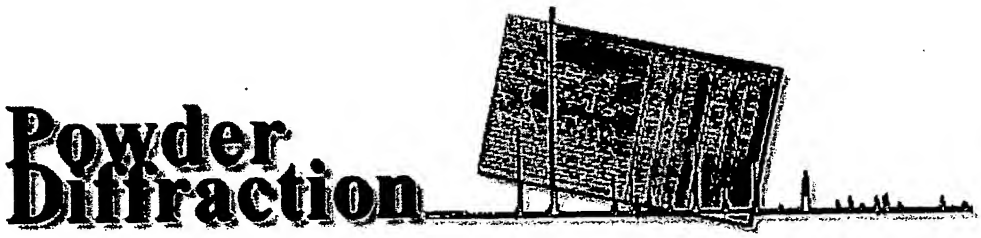
Statement of no new matter added in specifications

Sir:

In response to the Office communication concerning "Office Action Summary on September 20, 2006, the applicant made amendments. There is no new matter added in this amendment.

Respectfully submitted,
Mai De Ltd.

By _____
Hui Min He-Huang
Tel: (508) 873-3038



Powder Diffraction -- March 2000 -- Volume 15, Issue 1, pp. 2-6

Quantitation of crystallinity in substantially amorphous pharmaceuticals and study of crystallization kinetics by X-ray powder diffractometry

Rahul Surana and Raj Suryanarayanan
College of Pharmacy, 308 Harvard Street SE, University of Minnesota, Minneapolis, Minnesota 55455

(Received 28 July 1999; accepted 1 September 1999)

The first object was to develop an X-ray diffractometric method for the detection and quantificati of crystalline sucrose when it occurs as a mixture with amorphous sucrose. Standards consistin amorphous sucrose physically mixed with 1 to 5 weight percent crystalline sucrose were prepar The sum of the background subtracted integrated intensities of the 12.7°2θ (6.94 Å) and 13.1°2 (6.73 Å) sucrose diffraction peaks were linearly related to the weight percent crystalline sucrose The limits of detection and quantitation of crystalline sucrose were 0.9% and 1.8% w/w, respectively. The second object was to study the kinetics of crystallization of sucrose as a funct of temperature (at 102, 105 and 110 °C under a water vapor pressure of 0 Torr) and water vapc pressure (17.4, 19.8 and 21.4 Torr at 27 °C). In all cases, the crystallization kinetics was best described by the Avrami-Erofe'ev model (three-dimensional nucleation). *©2000 International Ce for Diffraction Data.*

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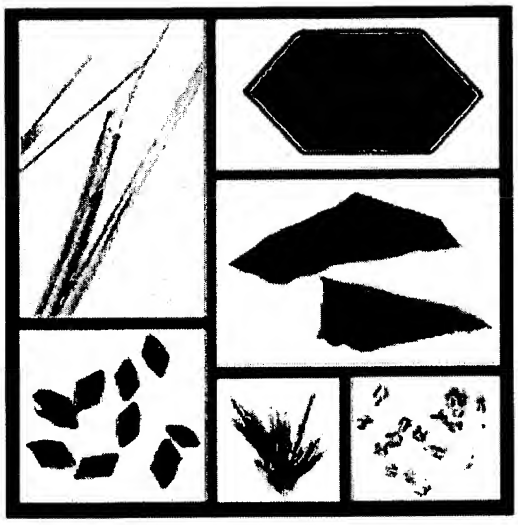
Week of Aug. 21, 2004; Vol. 166, No. 8 , p. 122

Tricky Business

The crystal form of a drug can be the secret to its success

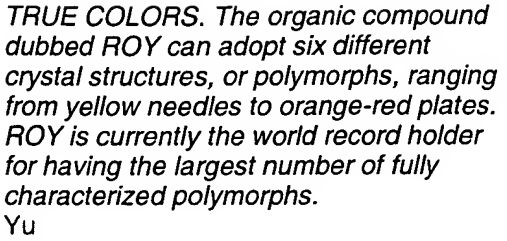
Alexandra Goho

In one of Kurt Vonnegut's science fiction novels, a scientist creates a form of ice that doesn't melt until it reaches 114.4°F. Called Ice-9, this imaginary crystal takes over the world, as all of Earth's waters, and life itself, freeze solid. What endows Ice-9 with such unusual properties is the unique configuration of the stacked water molecules. Although Ice-9 of *Cat's Cradle* (1963, Holt, Rinehart and Winston) is pure fantasy, the concept of a molecule assuming multiple crystal structures—or polymorphs—is real, and the consequences can be dramatic. One polymorph of carbon provides black and slippery graphite, another is hard, transparent diamond. A blue pigment used in ink-jet printers has either a red or green tint, depending on the pigment's crystal structure. Even crystallized cocoa butter has different polymorphs; some cause the chocolate to melt in your mouth more quickly than others.



In recent years, the pharmaceutical industry has increasingly focused its attention on polymorphs. There's plenty of incentive. The precise arrangement of molecules within the crystal of a drug determines how fast it dissolves in the body and how much enters the bloodstream. Polymorphs of a drug differ in properties that affect its

shelf life or ease of manufacture. A newly discovered polymorph may turn out to be a more effective and convenient than the original product.



TRUE COLORS. The organic compound dubbed ROY can adopt six different crystal structures, or polymorphs, ranging from yellow needles to orange-red plates. ROY is currently the world record holder for having the largest number of fully characterized polymorphs.
Yu

The Food and Drug Administration requires all companies to register the precise polymorph of any drug that they produce. Pharmaceutical manufacturers also have to demonstrate that each polymorph is stable and can be reproduced reliably. Otherwise, it would be hard to set a drug's effective dosage. "The FDA has very strict regulations on this," says Jerry Atwood of the University of Missouri-Columbia.

Regulations aside, drug companies are becoming increasingly aware that different polymorphs can translate into more or less profit. Because each polymorph is legally defined as a unique, patentable composition of matter, a company that develops a new drug will patent all the polymorphs that it has discovered and produced.

That, however, affords the patent holder only limited business protection. Because the science behind polymorphs remains murky, there's no guarantee that a competitor won't discover a new polymorph of the drug that's better than the patented ones.

The world of polymorphs also opens up complicated business strategies. For example, when a patent is set to expire, a company might have other patents related to a drug's polymorphs that make it difficult for competitors to produce generic versions.

Situations such as these have fueled intense litigation over the years. "The polymorph issue is so important to the pharmaceutical industry," says Atwood. "We're talking about multibillion-dollar drugs. Ultimately, it comes down to a hard legal battle."

It also comes down to fundamental chemistry. Polymorphism has elicited enough excitement and fear in the drug business that a growing number of researchers in academia and in private companies are taking a closer look at how crystals grow, and what these scientists discover could shape an entire industry.

Disappearing act

Emblematic of the importance of polymorphs is the cautionary tale of ritonavir, the AIDS drug made by Abbott Laboratories.

Introduced in 1996, the drug had been on the market for 18 months when suddenly, during manufacturing, chemical engineers detected a previously unknown polymorph. No one knew what had caused the change, but the scientists discovered that the new polymorph was thermodynamically stabler than the drug in its original form. The Abbott team couldn't find a way to stop formation of the new polymorph. Within a few days of its discovery, this new polymorph was dominating the product coming off the lines, says Sanjay Chemburkar, one of the Abbott chemists involved in the situation.

Although the two polymorphs shared a chemical formula, their structural dissimilarity made a difference to patients. The second form was only half as soluble as the first, so patients taking prescribed doses wouldn't get enough of the drug into their bloodstreams. Abbott pulled ritonavir from the market.

"The company went on a crash program to try to get their [original] polymorph back," says Atwood. Abbott eventually succeeded in producing the first form again, but it could not make the polymorph reliably and kept getting mixtures of the two forms. The company finally decided to reformulate the drug in the second polymorphic form as a liquid gel capsule containing the predissolved drug. Unlike the original formulation of the drug, the gel capsules require refrigeration.

"Abbott lost a lot of money over this," says Allan Myerson of the Illinois Institute of Technology in Chicago. The company spent hundreds of millions of dollars trying to recover the first polymorph and lost an estimated $250 million in sales the year the drug was withdrawn.

Cases such as this aren't routine, but they're common enough for drug companies to be concerned about the surprises that polymorphism can bring, says Myerson.

Screening for polymorphs early on is always best, says Patrick Stahly. He's the chief operating officer at SSCI, a contract research laboratory in West Lafayette, Ind., that specializes in crystal screening and analysis. Even so, drug companies often wait until late in the development process before thoroughly screening for polymorphs. "We've had clients come to us in the middle of human clinical trials after discovering their drug had two different polymorphs," says Stahly. Such a company has to regain control over its manufacturing process and start the trials over using a single polymorph.

That experience underscores one way that companies can get bitten by polymorphism. There are other potential pitfalls as

well.

Consider ranitidine hydrochloride, the anti-ulcer drug owned by the drug giant GlaxoSmithKline and known by millions as Zantac. In the mid-1990s, as the patent on the drug was approaching expiration, other companies began gearing up to market cheaper, generic versions. By marketing drugs that have gone off patent, generics manufacturers skip human trials, the most expensive part of the drug-development process.

However, GlaxoSmithKline—which was simply Glaxo at the time—had in its pocket a patent on a second polymorph of the drug. The company discovered that second form early in the processing of the first form. Glaxo didn't receive a patent on the second form until nearly 7 years after receiving the initial drug patent. Because the second form was easier to manufacture, it became the active ingredient in Zantac.

Although other companies were legally permitted to make and sell generic versions of the first polymorph of ranitidine hydrochloride, they had to figure out how to make it without any contamination from the second, whose patent protection remained in force. This kept the generic companies products off the market for several years.

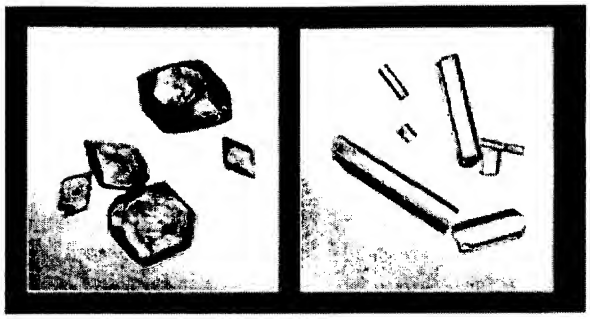
"Zantac was the largest-selling drug in the world," says Joel Bernstein of Ben-Gurion University of the Negev in Beer Sheva, Israel. Bernstein was an expert witness for Glaxo when a dispute over its original patent went to court. Glaxo was making $10 million in sales each day on its ulcer treatment, so every day it retained control over its drug was significant.

Crystal fate

The conventional approach to finding polymorphs begins with old-fashioned crystallization experiments. First, dissolve the drug in a solvent. Next, cool the solution or evaporate the solvent, coercing the drug molecules to stick together to form crystals. Varying the temperature of the solution and using different solvents are among the long-used tricks for getting the molecules to stack in different geometries.

Trying to discover new polymorphs in the lab can be frustrating. "Sometimes they show up, sometimes they don't," says Adam Matzger of the

University of Michigan in Ann Arbor. "There is very little in the way of new approaches to finding polymorphs."



POLYMER RELIEF. Growing crystals of the pain-relieving drug acetaminophen on different polymer surfaces will yield different crystal structures. One polymer gives rise to tiny prisms (left); another, miniature monoliths (right). Z. Tolstyka

In search of ideas, researchers have been exploring factors other than temperature and solvent that might influence crystallization and produce polymorphs. For instance, SSCI is investigating a technique developed by Myerson. Two years ago, he and his colleagues found that intense pulses of near-infrared light could affect the crystallization of the amino acid glycine. When the light was linearly polarized, so that its electric field vibrated in one direction, the crystal grew as one polymorph; when the light was circularly polarized, so that the electric field rotated, it induced a second polymorph.

Myerson suspects that the electric field generated by the light influences how the glycine molecules arrange themselves as they aggregate into small clusters early in the crystallization process.

The instructions for growing into a particular type of polymorph are imprinted on the cluster by the time it reaches a critical size containing tens to hundreds of molecules. Once these nuclei form, the "fate of the system has been decided," says Michael Ward of the University of Minnesota in Minneapolis.

Different packings of molecules lead to nuclei of different sizes, which in turn yield different polymorphs. So, Ward wondered whether confining a dissolved compound to a given space would limit the size of a nucleus that could form and force the molecules to pack in a specific polymorphic arrangement. As they reported in the March 24 *Journal of the American Chemical Society*, he and his colleagues tested this hypothesis by growing crystals within porous materials.

The Minnesota team turned to blocks of polymer with cylindrical pores 30 nanometers in diameter. To this material, the researchers added a solution of an organic chemical commonly used in the manufacture of pharmaceuticals. This compound, dubbed ROY, is currently the world record holder for having the most—six—fully characterized polymorphs. However, Ward and his colleagues found that only one form of ROY crystallized

inside the pores.

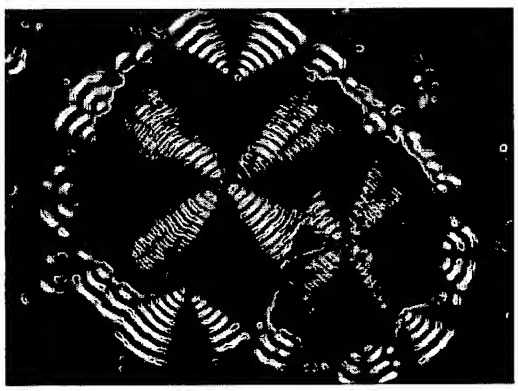
Ward notes that the fine details of surfaces also play a role in crystallization. Think of rock candy. "When you dissolve sugar in water and put a stick in the container, where does the candy grow? On the stick," he says.

Matzger, for one, has found that growing crystals of the same compound on different polymer materials can produce different polymorphs. The Michigan group crystallized the pain-relieving drug acetaminophen, which is known to have two polymorphs, on 84 different polymer materials. They found that certain materials, such as nylon and polyvinyl chloride—the plastic used in plumbing—induced one form to grow, while other polymers, such as cellulose, favored the other form.

Next, the researchers did a similar experiment with carbamazepine, an antiepileptic drug with three known crystal structures. Not only did all three polymorphs show up, but also a new and previously unknown polymorph grew on 4 of the 84 polymers. Matzger speculates that the precise way in which a polymer's atoms are arranged near the surface could favor the growth of certain polymorphs.

While pharmaceutical firms might use strategies like these to discover new polymorphs, once a company lands on a desirable crystal form of a drug, it faces other challenges. To make large quantities, researchers often seed batches of the dissolved drug with a small grain of the desired polymorph, expecting the grain to nucleate the growth of much larger crystals of the same polymorph.

That strategy usually works, but sometimes it doesn't. "The engineers will often say to me: 'The polymorphism of this drug is out of control. I seed with this crystal and I get something else,'" says pharmaceutical chemist Lian Yu.



BAD SEED. Two different polymorphs of the sugar mannitol were detected with a spectral-imaging technique. The two crystal structures scatter radiation differently, producing a unique pattern of black and white bands. The image shows how one polymorph of mannitol (inner pattern) can cause a second polymorph (outer pattern) to grow on its surface.

While working at Eli Lilly and Company in Indianapolis, Ind., Yu discovered that the surface of one crystal structure sometimes induces a different polymorph. In the

May 28, 2003 *Journal of the American Chemical Society*, Yu describes an experiment in which he used a polymorph of the sugar mannitol to seed a dissolved solution of the sugar. The polymorph that started forming on the surface of that crystal was a different one altogether. *J. Am. Chem. Soc.*

Yu, who is now at the University of Wisconsin–Madison, suspects that this process could be at the heart of many incidents, such as Abbott's ritonavir saga, in which researchers at drug-manufacturing plants suddenly find they can no longer grow the polymorph they want. Some unrecognized change in the manufacturing process might have altered whether the growing crystals model themselves after their seed crystals.

Forecasting

In 1965, a Chicago microscopist named Walter C. McCrone stated the following maxim regarding the art of crystal growing: "The number of forms known for a given compound is proportional to the time and money spent in research on that compound."

Consider ROY. It took Yu and his colleagues many years to produce all six forms, which they first reported in 2000. The colorful diversity of the different crystal structures—which range from red needles to orange plates to yellow prisms—and the fact that they all form at room temperature "really has captured the imagination of the community," says Yu.

Other compounds, however, do not support McCrone's rule. Aspirin, for example, has been crystallized by the tons for decades under many different conditions, and yet only one crystal form has ever emerged, says Sally Price at University College London. "People are fairly confident that there aren't any more to be found," she says.

Yet without extensive studies, there is no way to entirely discount the possibility that some sets of conditions could lead to polymorphs of aspirin. "Right now, you can't predict polymorphs, and you can't predict their properties," says Atwood.

Such forecasting might be possible in the future. Last fall, Price and her collaborators launched a multimillion-dollar research initiative to develop computer software tools that consider the arrangement of atoms within a compound to predict whether that compound is likely to take on different crystal structures and, if so, approximately how many.

A company might use such predictions to find that one of its drug molecules has other stable polymorphs. If so, the company would aggressively search for those polymorphs. The predicted crystal structures would also give researchers ideas for methods to produce the polymorphs in the lab.

Alternatively, the predictions might suggest that the polymorph in hand is the stablest form and that other forms are unlikely to arise. The company could then save the time and money that would otherwise be spent on unnecessary screening experiments.

At the moment, Price says her team can make predictions only for very simple molecules. "Most pharmaceuticals are far more complicated," she says. It could be a decade before such computer predictions can be applied to drug development. In the meantime, the specter of sudden polymorphism will remain a fact of life for pharmaceutical firms.

If you have a comment on this article that you would like considered for publication in *Science News*, send it to editors@sciencenews.org. Please include your name and location.

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Sources:

Jerry Atwood
Department of Chemistry
University of Missouri, Columbia
601 South College Avenue
Columbia, MO 65211

Joel Bernstein
Department of Chemistry
Ben-Gurion University of the Negev
P.O. Box 563
Beer-Sheva 84105
Israel

Sanjay R. Chemburkar
Process Development and Analytical Research
Abbott Laboratories
1401 Sheridan Road
North Chicago, IL 60064-6291

Adam Matzger
Department of Chemistry
University of Michigan, Ann Arbor
930 N. University
Ann Arbor, MI 48109-1055

Allan Myerson
Department of Chemical and Environmental Engineering
Illinois Institute of Technology
Room 103 Siegel Hall
Chicago, IL 60616-3793

Sally L. Price

Centre for Theoretical and Computational Chemistry
Department of Chemistry
University College London
20 Gordon Street
London WC1H 0AJ
United Kingdom

Patrick Stahly
SSCI, Inc.
3065 Kent Avenue
West Lafayette, IN 47906-1076

Michael Ward
Department of Chemical Engineering and Materials Science
University of Minnesota
Amundson Hall
421 Washington Avenue, SE
Minneapolis, MN 55455

Lian Yu
School of Pharmacy
University of Wisconsin, Madison
777 Highland Avenue
Madison, WI 53705-2222

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